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Progress Report

Evaluating bevacizumab in combination with FOLFIRI after the failure of platinum-etoposide regimen in patients with advanced poorly differentiated neuroendocrine carcinoma: The PRODIGE 41–BEVANEC randomized phase II study

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ABSTRACT

Introduction: Patients with gastroenteropancreatic (GEP), metastatic or locally advanced, non-resectable, grade 3 poorly-differentiated neuroendocrine carcinoma (NEC) are treated with cisplatin (or carboplatin)-etoposide in first-line palliative chemotherapy (CT1). However, nearly all patients will develop resistance and there is no standard second-line treatment.
Aim: PRODIGE 41–BEVANEC is an academic randomized, phase II study designed to evaluate the efficacy of bevacizumab in combination with FOLFIRI after failure of CT1 in unknown primary NEC and GEP-NEC.
Materials and methods: The main eligibility criteria are age ≥18 years, metastatic (synchronous or metachronous) or locally advanced, non-resectable, grade 3 GEP-NEC, and documented progressive disease during or after CT1 therapy.
Results: A total of 124 patients will be randomly assigned (1:1) to receive either 5 mg/kg bevacizumab with FOLFIRI, or FOLFIRI alone, every 14 days until disease progression or unacceptable toxicity.

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The hypothesis is to demonstrate a 6-month overall survival for at least 50% of the patients in bevacizumab arm versus 35% in the control arm (FOLFIRI alone). Secondary endpoints are objective response, response duration, progression-free survival, toxicity, and biochemical response.
Conclusion: The study is currently opened in France (NCT02820857). The first patient was randomized on September 6, 2017.

1. Rational and aims

Poorly differentiated neuroendocrine carcinomas (NEC) are a minority sub-group of digestive neuroendocrine neoplasms representing between 7 and 21% of patients [1–3]. Their diagnosis is based on a poorly differentiated cell morphology and the demonstration of the neuroendocrine nature of tumor cells by the expression of specific markers; proliferative capacities are usually high, corresponding to a histological grade 3 [4]. Recent data on the initial presentation of gastroentero-pancreatic neuroendocrine carcinomas (GEP-NEC) have been reported in two retrospective and one prospective studies [5–7]. The two studies focusing on GEP-NECs and excluding grade 3 NETs [5,6] found that less than 2% of GEP-NECs presented a functional tumor. The main primary locations were gastroesophageal (18% and 13% of cases respectively), duodenopancreatic (29%/29%), colorectal (28%/31%), unknown (20%/15%) or other gastrointestinal primary cancer (5%/12%). Seventy-nine and 87% of GEP-NECs were metastatic at diagnosis. Histologically, and contrary to bronchial NECs, large-cell GEP-NECs (61%/57%) were more frequent than small-cell GEP-NEC (39%/43%), and the median proliferation index Ki-67 was 75% and 80% respectively [5,6]. The spontaneous prognosis for patients suffering from NECs remains poor, with median survivals around 11–17 months [5–7]. Performance status, stage and high serum level of chromogranin A, neuron-specific enolase (NSE), and lactate dehydrogenase (LDH) are poor prognostic factors [5–7].

The French National Institute of Cancer (Institut National du Cancer — INCa) recommends that all medical files of patients suffering from GEP-NEC should be discussed in the regional multidisciplinary tumor board meetings that are part of the national network dedicated to neuroendocrine tumor (RENATEN network). In parallel, the pathology specimen must be reviewed by the network of expert pathologists (TENpath network). The French recommendations for the treatment of GEP-NECs are regularly updated [8]. They are included in the national thesaurus for digestive oncology (TNCD) (www.tncd.org). The rarity of the pathology explains the low level of proof for the recommendations which, with regards to the GEP-NEC, are essentially expert-based opinions. There are very few clinical trials that have investigated GEP-NEC and no phase III study (for review see Sorbye et al. [9]). Several retrospective series, often single center and having included a small number of patients, are the only studies carried out on the second-line treatment of GEP-NECs [7,10–13]. At present, two other phase II studies investigating second-line treatment of GEP-NECs are registered in clinicaltrial.gov; one concerns the safety and tolerability of everolimus (National Clinical Trial identifier NCT02113800) and the other the efficacy of avelumab (NCT03147404). A French study, evaluating sunitinib in GEP-NECs with the objective of identifying predictive molecular markers of response to sunitinib (NCT01215578), is now closed to inclusions but its results are not yet published.

The chemosensitivity of these tumors is very high with an objective response rate varying from 41 to 75% [14,15]. However, the median duration of the response is only 8–9 months and almost all patients will develop early secondary resistance that leads to a median survival of 15–19 months. In cases of a progressive recurrence more than 6 months after the end of the first-line treatment by etoposide and platinum, the resumption of the same treatment is recommended. In case of earlier recurrence, in particular <3 months, a second-line chemotherapy is recommended for patients whose general state remains relatively good. Three regimens have been proposed: FOLFIRI [10], FOLFOX/CAPOX [11], or temozolomide-based regimens [12,13,16]. However, the progression-free survival observed with these regimens is always lower than 3–4 months. In small-cell bronchial cancers, topotecan is approved as a second-line treatment but does not seem to be effective in digestive NEC [17]. The overall survival from the second-line treatment is 3.5–9.5 months [9,13]. Bevacizumab associated with a cytotoxic chemotherapy has shown promising results in well differentiated NETs (BETTER trials, [18,19]). Moreover, the angiogenesis is more pronounced in NEC than in NETs [20]. The efficacy of bevacizumab has also been suggested in patients with GEP-NEC [12,16,21], but never as part of a phase II trial. Because of this background and as bevacizumab associated with FOLFIRI is reported to be efficient and well tolerated in metastatic colorectal cancer [22], we therefore set out to investigate the contribution of bevacizumab added to FOLFIRI versus FOLFIRI alone administered as second-line treatment.

2. Study design

The PRODIGE 41–BEVANEC is a national, multicenter, randomized non-comparative phase II study assessing the safety and efficacy of the combination FOLFIRI-bevacizumab versus FOLFIRI after the failure of platinum-etoposide in patients suffering from progressive NEC (of a gastrointestinal or unknown primary cancer). The patients will be followed until death, and for a minimum of 6 months after the beginning of treatment. The choice of a randomized (1:1) phase II study assessing the tolerance and efficacy of FOLFIRI-bevacizumab versus FOLFIRI is based on several concepts: FOLFIRI is the most prescribed second-line treatment in France and is recommended by the TNCD [5,8]; however, the efficacy of FOLFIRI is based on a poor level of proof (no prospective phase II study in this population), therefore the use of control arm will allow to confirm its effect.

This study includes (i) patients aged 18 years or more with an NEC (according to the WHO 2010) from a GEP or unknown primary cancer that is locally advanced and/or metastatic, with a centralized review of the diagnosis by a consulting pathologist specializing in NET (TENPath network), and (ii) with disease progression (using the RECIST criteria v.1.1) while on/or within the 6 months following the discontinuation of cisplatin (or carboplatin) and etoposide chemotherapy. All patients must have a performance status ≤2 (WHO) and have given their written consent for participation in this trial. Patients are not eligible for this study if any of the following exclusion criteria applies: well differentiated GEP-NET, mixed tumor, first-line chemotherapy other than cisplatin (or carboplatin) and etoposide; pulmonary or non-digestive NEC; contraindication to FOLFIRI; contraindication to bevacizumab.

FOLFIRI is given every 2 weeks according to the following schedule: 180 mg/m^2 irinotecan by intravenous infusion over

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